We Claim:

1. A method of identifying a compound that reduces whole body insulin sensitivity of an animal, said method comprising: (a) administering a compound to a non-human animal, isolated tissue or isolated cell having reduced expression of functional Cbl compared to an otherwise isogenic wild-type animal, tissue or cell; and (b) determining the activity of acetyl CoA carboxylase (ACC) and/or amount of phosphorylated ACC enzyme in the animal, tissue or cell wherein a reduced amount of phosphorylated ACC enzyme and/or enhanced activity of an ACC enzyme compared to the amount of phosphorylated ACC enzyme or activity of an ACC enzyme of a Cbl-deficient animal, tissue or cell to which the compound has not been administered indicates that the compound reduces whole body insulin sensitivity in an animal.

2. The method of claim 1 wherein ACC activity is determined by a process comprising measuring the incorporation of labeled carbon into malonyl CoA in the presence and absence of the compound.

3. The method of claim 1 wherein phosphorylated ACC is determined by contacting cells or a cell extract with an antibody that binds to the phosphorylated form of the enzyme under conditions sufficient for an antigen-antibody complex to form and detecting the antibody bound.

4. The method of claim 3 further comprising separately contacting cells or cell extract with an antibody that binds to non-phosphorylated ACC under conditions sufficient for an antigen-antibody complex to form and detecting the antibody bound.

5. The method of claim 3 or 4 wherein detecting the antibody bound comprises contacting the antibody with a secondary antibody that is capable of producing a detectable signal.

6. The method of claim 1 further comprising determining the percentage of phosphorylated ACC relative to total ACC in the sample in the presence and absence of the compound being tested.

7. The method according to claim 1 wherein the non-human animal is a mammal.

8. The method according to claim 7 wherein the mammal is selected from the group consisting of rodent, dog, pig, bovine, sheep, horse and goat.

9. The method according to claim 8 wherein the rodent is selected from the group consisting of rabbit, rat, guinea pig and mouse.

10. The method according to claim 9 wherein the rodent is a mouse.

11. The method of claim 1 wherein the cells are skeletal muscle cells, cardiac myoblasts or adipocytes.

12. The method according to claim 1 wherein the animal, tissue or cell has reduced expression of functional Cbl by virtue of a targeted disruption of at least one endogenous Cbl allele.

13. The method of claim 12 wherein the animal, tissue or cell has expression of both Cbl alleles disrupted.

14. The method of claim 1 wherein the animal, tissue or cell has reduced expression of functional Cbl by virtue of carrying an inhibitory molecule that reduces endogenous Cbl expression.

15. The method according to claim 14 wherein the inhibitory molecule is a dominant negative mutant of Cbl.

16. The method according to claim 15 wherein the dominant negative mutant of Cbl comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 250, SEQ ID NO: 252, SEQ ID NO: 254, SEQ ID NO: 256, SEQ ID NO: 258, SEQ ID NO: 260 and SEQ ID NO: 262.

17. The method according to claim 14 wherein the inhibitory molecule comprises an antisense molecule, ribozyme, siRNA, or shRNA.

18. The method according to claim 17 wherein the siRNA or shRNA comprises a nucleotide sequence set forth in any one of SEQ ID NOS: 6-241 or 268.

19. The method according to claim 18 wherein the shRNA comprises the nucleotide sequence set forth in SEQ ID NO: 268.

20. The method according to claim 1 wherein the compound is administered to muscle tissue of an animal subject.

21. The method of claim 1 further comprising:
(i) optionally, determining the structure of the compound; and
(ii) providing the compound or the name or structure of the compound.

22. The method of claim 21 comprising providing the compound or the name or structure of the compound with an indication as to its use.

23. The method of claim 21 further comprising producing or synthesizing the compound.

24. A method of identifying a compound that enhances whole body insulin sensitivity of an animal comprising: (a) administering a compound to a non-human animal, isolated tissue or isolated cell expressing a functional Cbl protein and determining the activity of acetyl CoA carboxylase (ACC) and/or amount of phosphorylated ACC enzyme; (b) determining the activity of ACC and/or amount of phosphorylated ACC enzyme in a non-human animal, isolated tissue or isolated cell having reduced expression of functional Cbl compared to an otherwise isogenic wild-type animal, tissue or cell; and (c) comparing the activity of ACC and/or amount of phosphorylated ACC enzyme at (a) and (b) wherein a comparable activity and/or amount of phosphorylated ACC enzyme between (a) and (b) indicates that the compound enhances whole body insulin sensitivity of an animal.

25. The method of claim 24 wherein ACC activity is determined by a process comprising by measuring the incorporation of labeled carbon into malonyl CoA in the presence and absence of the compound.

26. The method of claim 23 wherein phosphorylated ACC is determined by contacting cells or a cell extract with an antibody that binds to the phosphorylated form of the enzyme under conditions sufficient for an antigen-antibody complex to form and detecting the antibody bound.

27. The method of claim 26 further comprising separately contacting cells or cell extract with an antibody that binds to non-phosphorylated ACC under conditions sufficient for an antigen-antibody complex to form and detecting the antibody bound.

28. The method of claim 26 or 27 wherein detecting the antibody bound comprises contacting the antibody with a secondary antibody that is capable of producing a detectable signal.

29. The method of claim 23 further comprising determining the percentage of phosphorylated ACC relative to total ACC in the sample in the presence and absence of the compound being tested.

30. The method according to claim 23 wherein the non-human animal is a mammal.

31. The method according to claim 30 wherein the mammal is selected from the group consisting of rodent, dog, pig, bovine, sheep, horse and goat.

32. The method according to claim 31 wherein the rodent is selected from the group consisting of rabbit, rat, guinea pig and mouse.

33. The method according to claim 32 wherein the rodent is a mouse.

34. The method of claim 23 wherein the cells are skeletal muscle cells, cardiac myoblasts or adipocytes.

35. The method according to claim 23 wherein the animal, tissue or cell expresses an endogenous functional Cbl.

36. The method of claim 23 wherein the animal, tissue or cell expresses and introduced Cbl gene.

37. The method of claim 36 wherein the animal, tissue or cell is non-human and expresses an introduced human Cbl gene.

38. The method according to claim 23 wherein the compound being tested is a peptidyl inhibitor of Cbl.

39. The method of claim 38 wherein the inhibitor is a dominant negative mutant of Cbl.

40. The method according to claim 39 wherein the dominant negative mutant of Cbl comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 250, SEQ ID NO: 252, SEQ ID NO: 254, SEQ ID NO: 256, SEQ ID NO: 258, SEQ ID NO: 260 and SEQ ID NO: 262.

41. The method according to claim 23 wherein the compound being tested comprises nucleic acid.

42. The method according to claim 41 wherein the nucleic acid comprises antisense nucleic acid, ribozyme, siRNA, or shRNA.

43. The method according to claim 42 wherein the siRNA or shRNA comprises a nucleotide sequence set forth in any one of SEQ ID NOS: 6-241.

44. The method according to claim 23 wherein the compound is administered to muscle tissue of an animal subject.

45. The method of claim 23 further comprising:
(i) optionally, determining the structure of the compound; and
(ii) providing the compound or the name or structure of the compound.

46. The method of claim 45 comprising providing the compound or the name or structure of the compound with an indication as to its use.

47. The method of claim 45 further comprising producing or synthesizing the compound.

48. A method of identifying a compound that reduces whole body insulin sensitivity of an animal, said method comprising: (a) administering a compound to a non-human animal, isolated tissue or isolated cell having reduced expression of functional Cbl compared to an otherwise isogenic wild-type animal, tissue or cell; and (b) determining the activity of AMP-dependent protein kinase (AMPK) and/or amount of phosphorylated AMPK enzyme in the animal, tissue or cell wherein a reduced amount of phosphorylated AMPK enzyme and/or reduced activity of AMPK enzyme compared to the amount of phosphorylated AMPK enzyme or activity of AMPK enzyme of a Cbl-deficient animal, tissue or cell to which the compound has not been administered indicates that the compound reduces whole body insulin sensitivity in an animal.

49. The method of claim 48 wherein AMPK activity is determined by a process comprising following the incorporation of labelled phosphate into a synthetic peptide SAMS in the presence and absence of the compound.

50. The method of claim 48 wherein phosphorylated AMPK is determined by contacting cells or a cell extract with an antibody that binds to the phosphorylated form of the enzyme under conditions sufficient for an antigen-antibody complex to form and detecting the antibody bound.

51. The method of claim 50 further comprising separately contacting cells or cell extract with an antibody that binds to non-phosphorylated AMPK under

conditions sufficient for an antigen-antibody complex to form and detecting the antibody bound.

52. The method of claim 50 or 51 wherein detecting the antibody bound comprises contacting the antibody with a secondary antibody that is capable of producing a detectable signal.

53. The method of claim 48 further comprising determining the percentage of phosphorylated AMPK relative to total AMPK in the sample in the presence and absence of the compound being tested.

54. The method according to claim 48 wherein the non-human animal is a mammal.

55. The method according to claim 54 wherein the mammal is selected from the group consisting of rodent, dog, pig, bovine, sheep, horse and goat.

56. The method according to claim 55 wherein the rodent is selected from the group consisting of rabbit, rat, guinea pig and mouse.

57. The method according to claim 56 wherein the rodent is a mouse.

58. The method of claim 48 wherein the cells are skeletal muscle cells, cardiac myoblasts or adipocytes.

59. The method according to claim 48 wherein the animal, tissue or cell has reduced expression of functional Cbl by virtue of a targeted disruption of at least one endogenous Cbl allele.

60. The method of claim 59 wherein the animal, tissue or cell has expression of both Cbl alleles disrupted.

61. The method of claim 60 wherein the animal, tissue or cell has reduced expression of functional Cbl by virtue of carrying an inhibitory molecule that reduces endogenous Cbl expression.

62. The method according to claim 61 wherein the inhibitory molecule is a dominant negative mutant of Cbl.

63. The method according to claim 62 wherein the dominant negative mutant of Cbl comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 250, SEQ ID NO: 252, SEQ ID NO: 254, SEQ ID NO: 256, SEQ ID NO: 258, SEQ ID NO: 260 and SEQ ID NO: 262.

64. The method according to claim 61 wherein the inhibitory molecule comprises an antisense molecule, ribozyme, siRNA, or shRNA.

65. The method according to claim 64 wherein the siRNA or shRNA comprises a nucleotide sequence set forth in any one of SEQ ID NOS: 6-241 or 268.

66. The method according to claim 65 wherein the shRNA comprises the nucleotide sequence set forth in SEQ ID NO: 268.

67. The method according to claim 48 wherein the compound is administered to muscle tissue of an animal subject.

68. The method of claim 48 further comprising:
(i) optionally, determining the structure of the compound; and
(ii) providing the compound or the name or structure of the compound.

69. The method of claim 68 comprising providing the compound or the name or structure of the compound with an indication as to its use.

70. The method of claim 69 further comprising producing or synthesizing the compound.

71. A method of identifying a compound that enhances whole body insulin sensitivity of an animal comprising: (a) administering a compound to a non-human animal, isolated tissue or isolated cell expressing a functional Cbl protein and determining the activity of AMP-dependent protein kinase (AMPK) and/or amount of phosphorylated AMPK enzyme; (b) determining the activity of AMPK and/or amount of phosphorylated AMPK enzyme in a non-human animal, isolated tissue or isolated cell having reduced expression of functional Cbl compared to an otherwise isogenic wild-type animal, tissue or cell; and (c) comparing the activity of AMPK and/or amount of phosphorylated AMPK enzyme at (a) and (b) wherein a comparable activity of AMPK and/or comparable amount of phosphorylated AMPK enzyme between (a) and (b) indicates that the compound enhances whole body insulin sensitivity of an animal.

72. The method of claim 71 wherein AMPK activity is determined by a process comprising following the incorporation of labelled phosphate into a synthetic peptide SAMS in the presence and absence of the compound.

73. The method of claim 71 wherein phosphorylated AMPK is determined by contacting cells or a cell extract with an antibody that binds to the phosphorylated form of the enzyme under conditions sufficient for an antigen-antibody complex to form and detecting the antibody bound.

74. The method of claim 73 further comprising separately contacting cells or cell extract with an antibody that binds to non-phosphorylated AMPK under conditions sufficient for an antigen-antibody complex to form and detecting the antibody bound.

75. The method of claim 73 or 74 wherein detecting the antibody bound comprises contacting the antibody with a secondary antibody that is capable of producing a detectable signal.

76. The method of claim 71 further comprising determining the percentage of phosphorylated AMPK relative to total AMPK in the sample in the presence and absence of the compound being tested.

77. The method according to claim 71 wherein the non-human animal is a mammal.

78. The method according to claim 77 wherein the mammal is selected from the group consisting of rodent, dog, pig, bovine, sheep, horse and goat.

79. The method according to claim 78 wherein the rodent is selected from the group consisting of rabbit, rat, guinea pig and mouse.

80. The method according to claim 79 wherein the rodent is a mouse.

81. The method of claim 71 wherein the cells are skeletal muscle cells, cardiac myoblasts or adipocytes.

82. The method according to claim 71 wherein the animal, tissue or cell expresses an endogenous functional Cbl.

83. The method of claim 71 wherein the animal, tissue or cell expresses an introduced Cbl gene.

84. The method of claim 83 wherein the animal, tissue or cell is non-human and expresses an introduced human Cbl gene.

85. The method according to claim 71 wherein the compound being tested is a peptidyl inhibitor of Cbl.

86. The method of claim 85 wherein the inhibitor is a dominant negative mutant of Cbl.

87. The method according to claim 86 wherein the dominant negative mutant of Cbl comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 250, SEQ ID NO: 252, SEQ ID NO: 254, SEQ ID NO: 256, SEQ ID NO: 258, SEQ ID NO: 260 and SEQ ID NO: 262.

88. The method according to claim 71 wherein the compound being tested comprises nucleic acid.

89. The method according to claim 88 wherein the nucleic acid comprises antisense nucleic acid, ribozyme, siRNA, or shRNA.

90. The method according to claim 89 wherein the siRNA or shRNA comprises a nucleotide sequence set forth in any one of SEQ ID NOS: 6-241.

91. The method according to claim 71 wherein the compound is administered to muscle tissue of an animal subject.

92. The method of claim 71 further comprising:
(i) optionally, determining the structure of the compound; and
(ii) providing the compound or the name or structure of the compound.

93. The method of claim 71 comprising providing the compound or the name or structure of the compound with an indication as to its use.

94. The method of claim 92 further comprising producing or synthesizing the compound.

95. A method of identifying a compound that reduces whole body insulin sensitivity of an animal, said method comprising: (a) administering a compound to a non-human animal, isolated tissue or isolated cell having reduced expression of functional Cbl compared to an otherwise isogenic wild-type animal, tissue or cell; and (b) determining free fatty acid level and/or fatty acid oxidation in the animal, tissue or cell, wherein enhanced free fatty acids and/or reduced fatty acid oxidation compared to free fatty acid level and/or fatty acid oxidation of a

Cbl-deficient animal, tissue or cell to which the compound has not been administered indicates that the compound reduced whole body insulin sensitivity of an animal.

96. A method of identifying a compound that enhances whole body insulin sensitivity of an animal, said method comprising: (a) administering a compound to a non-human animal, isolated tissue or isolated cell expressing a functional Cbl protein and determining free fatty acid level and/or fatty acid oxidation in the animal, tissue or cell; (b) determining free fatty acid level and/or fatty acid oxidation in a non-human animal, isolated tissue or isolated cell having reduced expression of functional Cbl compared to an otherwise isogenic wild-type animal, tissue or cell; and (c) comparing free fatty acid level and/or fatty acid oxidation at (a) and (b) wherein a comparable free fatty acid level and/or fatty acid oxidation between (a) and (b) indicates that the compound enhances whole body insulin sensitivity of an animal.

97. A method of identifying a therapeutic target for the treatment of aberrant insulin action or a condition associated therewith, said method comprising administering to an animal, tissue or cell a compound capable of reducing the expression and/or activity of a Cbl protein and determining the activity and/or expression of one or more genes and/or proteins in the animal, tissue or cell wherein modified expression and/or activity of a gene or protein indicates that the gene or protein is a therapeutic target for the treatment of aberrant insulin action or a condition associated therewith.

98. The method of claim 97 wherein the animal is a mammal.

99. The method according to claim 98 wherein the mammal is selected from the group consisting of rodent, dog, pig, bovine, sheep, horse and goat.

100. The method according to claim 99 wherein the rodent is selected from the group consisting of rabbit, rat, guinea pig and mouse.

101. The method according to claim 100 wherein the rodent is a mouse.

102. The method of claim 97 wherein the cells are skeletal muscle cells, cardiac myoblasts or adipocytes.

103. The method of claim 102 wherein the cells are myoblasts.

104. The method according to claim 97 wherein the compound is a peptidyl inhibitor of Cbl.

105. The method of claim 104 wherein the inhibitor is a dominant negative mutant of Cbl.

106. The method according to claim 105 wherein the dominant negative mutant of Cbl comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 250, SEQ ID NO: 252, SEQ ID NO: 254, SEQ ID NO: 256, SEQ ID NO: 258, SEQ ID NO: 260 and SEQ ID NO: 262.

107. The method according to claim 97 wherein the compound comprises nucleic acid.

108. The method of claim 107 wherein the nucleic acid comprises a targeting vector capable of disrupting expression of at least one endogenous Cbl allele.

109. The method according to claim 107 wherein the nucleic acid comprises antisense nucleic acid, ribozyme, siRNA, or shRNA.

110. The method according to claim 109 wherein the siRNA or shRNA comprises a nucleotide sequence set forth in any one of SEQ ID NOS: 6-241 or 268.

111. The method of claim 110 wherein the shRNA comprises the nucleotide sequence set forth in SEQ ID NO: 268.

112. The method according to claim 97 wherein the compound is administered to muscle tissue of an animal subject.

113. The method of claim 97 further comprising identifying a compound that modulates the expression or activity of the therapeutic target.

114. A method of identifying a compound that reduces mitochondrial ACC enzyme activity comprising determining the level of Cbl expression and/or activity in the presence and absence of the compound wherein enhanced expression and/or activity of Cbl in the presence of the compound indicates that the compound reduces mitochondrial ACC enzyme activity.

115. A method of identifying a compound that enhances mitochondrial ACC enzyme activity comprising determining the level of Cbl expression and/or activity in the presence and absence of the compound wherein reduced expression and/or activity of Cbl in the presence of the compound indicates that the compound enhances mitochondrial ACC enzyme activity.

116. A method of identifying a compound that reduces mitochondrial AMPK enzyme activity comprising determining the level of Cbl expression and/or activity in the presence and absence of the compound wherein enhanced expression and/or activity of Cbl in the presence of the compound indicates that the compound reduces mitochondrial AMPK enzyme activity.

117. A method of identifying a compound that enhances mitochondrial AMPK enzyme activity comprising determining the level of Cbl expression and/or activity in the presence and absence of the compound wherein reduced expression and/or activity of Cbl in the presence of the compound indicates that the compound enhances mitochondrial AMPK enzyme activity.

118. A method of identifying a compound that enhances free fatty acid synthesis comprising determining the level of Cbl expression and/or activity in the presence and absence of the compound wherein enhanced expression and/or activity of Cbl in the presence of the compound indicates that the compound enhances free fatty acid synthesis.

119. A method of identifying a compound that reduces free fatty acid synthesis comprising determining the level of Cbl expression and/or activity in the presence and absence of the compound wherein reduced expression and/or activity of Cbl in the presence of the compound indicates that the compound reduces free fatty acid synthesis.

120. A method of identifying a compound that reduces fatty acid oxidation comprising determining the level of Cbl expression and/or activity in the presence and absence of the compound wherein enhanced expression and/or activity of Cbl in the presence of the compound indicates that the compound reduces fatty acid oxidation.

121. A method of identifying a compound that enhances fatty acid oxidation comprising determining the level of Cbl expression and/or activity in the presence and absence of the compound wherein reduced expression and/or activity of Cbl in the presence of the compound indicates that the compound enhances fatty acid oxidation.

122. A method of identifying a compound that reduces expression of mitochondrial uncoupling protein 3 (UCP3) comprising determining the level of Cbl expression and/or activity in the presence and absence of the compound wherein enhanced expression and/or activity of Cbl in the presence of the compound indicates that the compound reduces UCP3 expression.

123. A method of identifying a compound that enhances expression of mitochondrial uncoupling protein 3 (UCP3) comprising determining the level of Cbl expression and/or activity in the presence and absence of the compound wherein reduced expression and/or activity of Cbl in the presence of the compound indicates that the compound enhances UCP3 expression.

124. A method of identifying a compound that reduces expression of an insulin receptor (IR) comprising determining the level of Cbl expression and/or activity in the presence and absence of the compound wherein enhanced expression

and/or activity of Cbl in the presence of the compound indicates that the compound reduces IR expression.

125. A method of identifying a compound that enhances expression of an insulin receptor (IR) comprising determining the level of Cbl expression and/or activity in the presence and absence of the compound wherein reduced expression and/or activity of Cbl in the presence of the compound indicates that the compound enhances IR expression.

126. The method according to any one of claims 114 to 125 wherein Cbl expression or activity is determined by a process comprising performing an immunoassay.

127. The method according to claim 126 comprising determining the amount of Cbl protein in the cell in the presence and absence of the compound.

128. The method of claim 126 comprising determining the level of c-Cbl-mediated ubiquitination of the insulin receptor in the presence and absence of the compound.

129. The method according to any one of claims 114 to 125 wherein Cbl expression or activity is determined by a process comprising determining phosphorylation of a tyrosine residue on Cbl protein in the presence and absence of the compound.